REMARKS

Upon entering the above amendment claims 1-3, 11, 13, 15-21 and 23-25 are pending in the present application. Applicants have canceled claims 14 and 22 with the above amendment and added new claim 26. Claims 1, 11 and 17 are independent claims.

Applicants have not raised any issue of new matter.

Applicants concurrently have filed a Request for Continued Examination (RCE) and wish the above amendment entered into the record and considered.

Foreign Priority

The Examiner reports that foreign priority documents have not been received. This application is a Division of U.S. Application 08/676,882, July 3, 1996, now U.S. Patent 6,100,241; therefore, Applicants respectfully request the Examiner to review the parent application to see if the certified foreign priority document is present. Applicants need to know, if 08/676,882 has an original foreign priority document in it file wrapper before Applicants can act.

Issue Under 35 U.S.C. §112, First Paragraph

Claims 3, 18, 23 and 24 stand rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly fails to

provide an enabling disclosure for any fragment of the isolated protein. The Examiner has maintained the same rejection. Applicants traverse this assertion.

As stated in previous responses, the specification clearly enables an isolated 37kd protein from Eimeria acervulina consisting of the amino acid sequence set forth in SEQ ID NO.:2 and a vaccine containing the 37kd protein.

The Examiner asserts that the present disclosure fails to provide enablement of fragments and the one fragment present, GWIKQEEVDDIVQK, is not enabled for its use as a vaccine. Again Applicants direct the Examiner to page 8, line 31 through page 9, line 2 and page 14, last paragraph where this issue is addressed.

Applicants have previously presented decision from the Federal Circuit that supports Applicants' assertion for enablement. Applicants have considered the list of requirements for enablement set forth by the Examiner. Applicants assert that the parameters set forth are not the law. The requirement of indication each of fragment that will retain activity of the intact protein is wrong. It is unreasonable that each fragment must be identified and tested.

More importantly, Applicants are not inviting one to experiment. Applicants have set forth one fragment as admitted by the Examiner. Applicants have set forth disclosure that a skilled artisan would need to understand how to locate, isolate or synthesize and use immunogenic determinant by indicating this

is done by Kyte-Doolittle plots, by Hopp-Woods plots and by surface-exposure plots of the Eimeria LDH. Proof of the effectivity of using such tools was provided pointing to the paper by Margalit et al (1987, J. of Immunol., vol. 138, p.2213-2229.

Applicants respectfully submit the publication by Schaap et al. (2004, Parasitology, vol. 128, p. 603-616). This journal article was published after the priority date of the application. Schaap et al. describes the cloning and the sequences of LDH's from the Eimeria species acervulina, tenella and maxima. The identity between the amino acid (aa) sequences is described as "rather low" and as "extensively diverged" being between 66 and 80% aa identity. A multiple alignment of the aa sequences is presented in figure 2 (p. 606). The aa sequence of E. tenella LDH was used to model its 3D structure, which was compared to that of Plasmodium falciparum (Malaria) LDH. Remarkably, the E. tenella and P. falciparum LDH proteins share only 47% aa identity but have an almost identical 3 dimensional structure (see figure 3, page 609). The article asserts on page 609 (bottom of left column - through top of right column): although the primary structure (the aa sequence) is "substantially different", their 3D structures are "very similar". Schaap et al. recite in the middle of that same page: "In summary . . . only shows 47% identity . . . conserved active site features . . . predicted to be a molecule with very similar properties."

Therefore, Applicants respectfully submit the following as facts:

-the patent application shows effective vaccination with E. acervulina LDH

-the publication by Schaap et al. show aa sequences of LDH protein of two more Eimeria species: tenella and maxima.

-these other two LDH proteins are "substantially different" in primary aa sequence: 66-80% identity.

-the 3D structure of the tenella LDH was predicted by computer modeling, and was compared to that of P. falciparum LDH

-the two 3D structures are "very similar"

-the primary aa sequence of the LDH proteins of E. tenella and P. falciparum are only 47% identical.

From these submitted facts, Applicants respectfully submit the following logical conclusions:

1. When two LDH proteins being so dissimilar as E. tenella and P. falciparum (47% identity) are found to have a very conserved 3D structure, then the three Eimeria LDH's which are much more related at the primary aa sequence level (66-80% identity) may be expected to be even more conserved in 3D structure.

2. It is common knowledge that a proteins 3D structure is important for immune-efficacy and the recognition of that protein by the immune system of a host-organism, consequently proteins

with a highly similar 3D structure will also be similar in their immunogenic properties

3. Consequently, as the E. acervulina LDH proved to be effective as a vaccine, therefore, the E. tenella and E. maxima LDH proteins, arguably having a 3D structure very similar to that of E. acervulina LDH, will also be effective in vaccines.

Applicants respectfully submit that the biological variants of E. acervulina LDH, such as the E. tenella and E. maxima LDH proteins, will be equally effective vaccines as the E. acervulina LDH.

Therefore, the present claims are enabled and would not lead to an undue burden of experimentation. The Examiner herself has presented alleged prior art that describe techniques known already in 1975 to determine size and specificity of *Eimeria* LDH enzymes in crude samples. Therefore, Applicants respectfully request withdrawal of the 35 U.S. §112, first paragraph rejection.

Issue Under 35 U.S.C. §102(b)

Claims 1-3, 11, 16-20 and 23-24 stand rejected under 35 U.S.C. §102(b) as being anticipated by Shirley (Parasitology, 71:369-376, 1975). Applicants assert that patentable distinction exists between the cited prior art and the present invention.

Distinction Between the Present Invention and Shirley

As presented in a previous response, Shirley allegedly discloses lactate dehydrogenase enzyme from E. acervulina. Shirley discloses a biochemical characterization of crude samples from Eimeria sporozoites, merozoites and oocysts. The characterization applied is starch-gel electrophoresis and substrate incubation.

The Examiner maintains an inherency argument that the isolated protein of the present invention is present within the mixture disclosed. Furthermore, the Examiner maintains that the vaccine claim is an intended use of the enzyme.

Shirley fails to disclose or suggest a protein expressed *in vitro*, comprising one or more immunoreactive and/or antigenic determinants of *Eimeria* lactate dehydrogenase (LDH), wherein said isolated protein is found intracellularly in Eimeria; a vaccine for the protection of poultry against Coccidiosis comprising an effective amount of an isolated protein comprising one or more immunoreactive and/or antigenic determinants of Eimeria lactate dehydrogenase, wherein said isolated protein is found intracellularly in Eimeria; and an immunogenic fragment of Eimeria lactate dehydrogenase (LDH), wherein said LDH is immunogenically reactive with antiserum raised against the polypeptide of SEQ ID NO:2.

Shirley, at best, discloses a native intact Eimeria LDH protein. Shirley never mentions using these proteins as

vaccines.

Applicants still completely disagree with Examiner's statement that the recitation of "vaccine" is an intended use. The vaccine claims stand alone. A vaccine claims can be clearly patentable, if is novel, even if the protein itself is anticipated. Shirley fails to discuss a vaccine; thus, it is completely impossible for Shirley to anticipate a "vaccine" claim.

Shirley fails to disclose each element of the present invention as set forth in the claims.

Applicants respectfully request withdrawal of the 35 U.S.C. §102(b).

Issue Under 35 U.S.C. §102(b)

Claims 1-3, 11, 16-18 and 23 stand rejected under 35 U.S.C. §102(b) as being anticipated by Kucera (Folia Parasitologica 36(4):295-299). Applicants assert that patentable distinction exists between the cited prior art and the present invention.

Distinction Between the Present Invention and Kucera

As presented in an earlier response, Kucera allegedly discloses lactate dehydrogenase enzyme from E. acervulina. Kucera discloses methods for performing techniques of Shirley (see above) with a certain type of electrophoresis equipment.

Homogenized Eimeria oocysts are used.

The Examiner maintains an inherency argument that the isolated protein of the present invention is present within the mixture disclosed. Furthermore, the Examiner maintains that the vaccine claim is an intended use of the enzyme.

Kucera fails to disclose or suggest a protein expressed *in vitro,* comprising one or more immunoreactive and/or antigenic determinants of *Eimeria* lactate dehydrogenase (LDH), wherein said isolated protein is found intracellularly in Eimeria; a vaccine for the protection of poultry against Coccidiosis comprising an effective amount of an isolated protein comprising one or more immunoreactive and/or antigenic determinants of Eimeria lactate dehydrogenase, wherein said isolated protein is found intracellularly in Eimeria; and an immunogenic fragment of Eimeria lactate dehydrogenase (LDH), wherein said LDH is immunogenically reactive with antiserum raised against the polypeptide of SEQ ID NO:2.

Kucera, at best, discloses a native intact Eimeria LDH protein. Kucera never mentions using these proteins as vaccines.

Again, Applicants completely disagree with Examiner's statement that the recitation of "vaccine" is an intended use. Kucera fails to discuss a vaccine; thus, it is completely impossible for Kucera to anticipate a "vaccine" claim.

Kucera fails to disclose each element of the present invention as set forth in the claims.

Applicants respectfully request withdrawal of the 35 U.S.C. §102(b).

Issue Under 35 U.S.C. §102(b)

Claims 1-3, 16-18 and 23 stand rejected under 35 U.S.C. §102(b) as being anticipated by Nakamura et al (Journal of Veterinary Medical Science, 53(6):1101-1103, 1991. Applicants assert that patentable distinction exists between the cited prior art and the present invention.

Distinction Between the Present Invention and Nakamura et al.

As previously presented, Nakamura et al. allegedly discloses lactate dehydrogenase enzyme from E. acervulina. Nakamura et al. discloses Eimeria enzyme starch-gel electrophoresis, and uses enzymes samples from sporulated oocysts.

The Examiner maintains an inherency argument that the isolated protein of the present invention is present within the mixture disclosed. Furthermore, the Examiner maintains that the vaccine claim is an intended use of the enzyme.

Nakamura et al. fails to disclose or suggest a protein expressed *in vitro*, comprising one or more immunoreactive and/or antigenic determinants of *Eimeria* lactate dehydrogenase (LDH), wherein said isolated protein is found intracellularly in Eimeria; a vaccine for the protection of poultry against

Coccidiosis comprising an effective amount of an isolated protein comprising one or more immunoreactive and/or antigenic determinants of Eimeria lactate dehydrogenase, wherein said isolated protein is found intracellularly in Eimeria; and an immunogenic fragment of Eimeria lactate dehydrogenase (LDH), wherein said LDH is immunogenically reactive with antiserum raised against the polypeptide of SEQ ID NO:2.

Nakamura et al., at best, discloses a native intact Eimeria LDH protein. Nakamura et al. never mentions using these proteins as vaccines.

Again, Applicants completely disagree with Examiner's statement that the recitation of "vaccine" is an intended use. Nakamura et al. fails to discuss vaccine; thus, it is completely impossible for Nakamura et al. to anticipate a "vaccine" claim.

Nakamura et al. fails to disclose each element of the present invention as set forth in the claims.

Applicants respectfully request withdrawal of the 35 U.S.C. §102(b).

Conclusion

All the stated grounds of the rejections have been properly traversed, accommodated or rendered moot. Applicants respectfully submit that the present application is in condition for allowance.

If the Examiner believes for any reason that personal

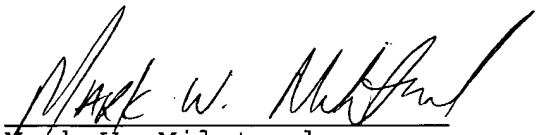
communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (302) 934-4395, in Millsboro, Delaware.

Pursuant to 37 C.F.R. §§1.17 and 1.136(a), Applicants respectfully petitions for a two month extension of time for filing a response in connection with the present application and the Commissioner is hereby authorized to charge the required fee of $420 to Deposit Account No. 02-2334.

If necessary, the Commissioner is hereby authorized in this, concurrent, and further replies, to charge payment or credit any overpayment to Deposit Account No. 02-2334 for any additional

fees required under 37 C.F.R. §1.16 or under 37 C.F.R. §1.17; particularly extension of time fees.

Respectfully submitted,



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Enclosure: Schaap et al. Journal Article